Pharmacokinetics and Safety of Obicetrapib in Moderate Hepatic Impairment: Phase I Study Results

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BACKGROUND

- Obicetrapib is a highly selective cholesteryl ester transfer protein (CETP) inhibitor in phase 3 development for the treatment of dyslipidemia[1]
- Drug clearance may be impaired in patients with hepatic impairment, underscoring the need to characterize a medication's pharmacokinetics in this population[2]
- Studies investigating obicetrapib metabolization and the potential involvement of efflux or uptake transporters in human hepatocytes, have to date, yielded inconclusive results[3]
- Therefore to determine appropriate dosing in cirrhosis, it is important to assess the pharmacokinetics of obicetrapib in patients with hepatic impairment compared with patients with normal hepatic function[2]

OBJECTIVE

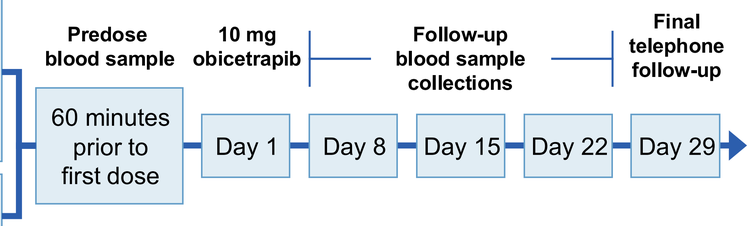
- This study aimed to determine how moderate hepatic impairment affects the pharmacokinetics, safety, and tolerability of a single 10 mg oral dose of obicetrapib compared with normal hepatic function

METHODS

Phase 1, open-label, nonrandomized, parallel-group study (NCT06048302) conducted between November 29, 2023, and March 20, 2024

Moderate hepatic impairment (n=10):
- Class B, modified Child-Pugh, mean score 7.7
- A diagnosis of hepatic dysfunction due to hepatocellular disease, stable hepatic impairment, and a stable drug regimen

Matched healthy controls (n=8):
- No hepatic impairment



- Plasma concentrations of obicetrapib were measured by MedPace Bioanalytical Laboratory (Cincinnati, OH). Pharmacokinetic parameters were analyzed using noncompartmental methods
- Safety assessments were considered secondary, assessed by adverse event, vital signs, physical examinations, laboratory tests, and 12-lead electrocardiograms

RESULTS AND DISCUSSION

- Demographic and baseline characteristics for all participants are shown in **Table 1**
- The concentration of obicetrapib pharmacokinetic (PK) parameters are shown in **Figure 1**
  - Median time to maximum plasma concentration (C_{max}) was similar between groups (6.0 hours vs 5.5 hours)
- A summary of all calculated obicetrapib PK parameters is provided in **Table 2**
  - Moderate hepatic impairment produced a lower C_{max} but higher $AUC_{0–t}$, a pattern most consistent with slower or reduced absorption combined with a prolonged terminal half-life, yielding modestly higher cumulative exposure despite a lower peak
- The statistical analysis of the primary PK parameters is reported in **Table 3**
  - Compared with healthy participants, those with moderate hepatic impairment exhibited lower C_{max}: geometric mean ratio of 71.58 (90% confidence interval [CI]: 60.23, 85.07), and higher area under the curve (area under the curve from time zero to time of last measurable concentration [AUC_{0-t}] and area under the curve from time zero to infinity [$AUC_{0-\infty}$]): 111.25 (90% CI: 90.12, 137.34) and 119.73 (90% CI: 93.87, 152.72), respectively
- Obicetrapib was safe and well tolerated in both groups
  - 2 participants experienced treatment-emergent adverse events (TEAEs): 1 participant in the moderate hepatic impairment cohort had mild abdominal pain not considered to be study related, and 1 participant in the normal hepatic function cohort had moderate diarrhea, mild flatulence, and nausea, all considered to be treatment related
  - No TEAE led to discontinuation of the study drug or removal from the study

Table 1. Demographic characteristics of subjects with moderate hepatic impairment and matched volunteers with normal hepatic function in the safety PK population*

Characteristic	Moderate Hepatic Impairment (n=9)	Normal Hepatic Function (n=8)
Age, years, mean ± SD	57.1 ± 5.40	58.3 ± 4.10
Sex, n (%)		
Male	5 (55.6)	6 (75.0)
Female	4 (44.4)	2 (25.0)
Ethnicity, n (%)		
Hispanic or Latino	7 (77.8)	4 (50.0)
Not Hispanic or Latino	2 (22.2)	4 (50.0)
Race, n (%)		
Black/African American	0	2 (25.0)
White	9 (100)	6 (75.0)
Height, cm, mean ± SD	165 ± 7.70	172 ± 7.21
Weight, kg, mean ± SD	84.9 ± 12.09	89.7 ± 8.25
Body mass index, kg/m^2, mean ± SD	31.4 ± 4.27	30.4 ± 2.78
Child-Pugh score, mean ± SD	7.7 ± 0.50	NA

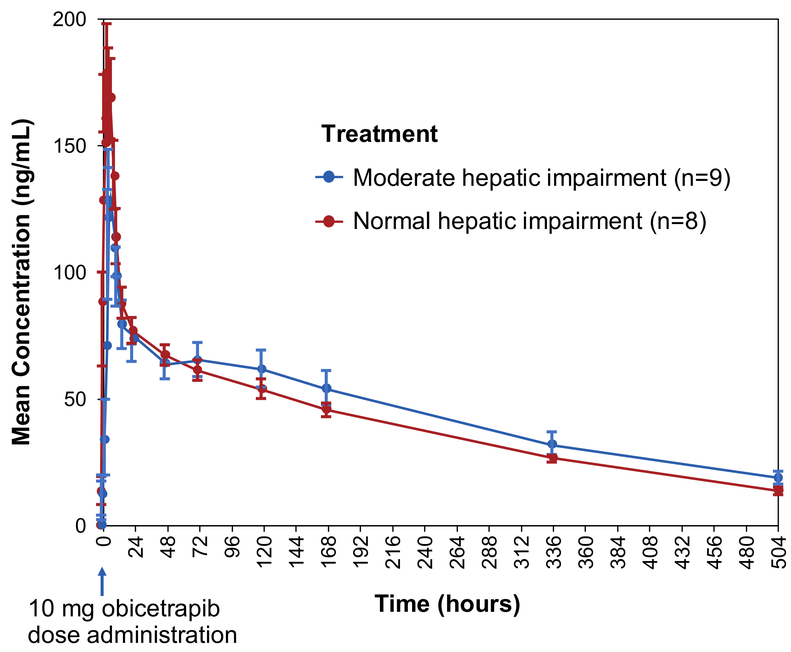
NA, not applicable; SD, standard deviation.
*One participant in the moderate hepatic impairment population did not have blood samples collected past the 48-hour blood draw and was not included in the PK population.

Table 2. Obicetrapib PK parameters in the PK population* for subjects with moderate hepatic impairment and matched volunteers with normal hepatic function

Characteristic	Moderate Hepatic Impairment (n=9)	Normal Hepatic Function (n=8)
C_{max} (ng/mL), mean ± SD	157.38 ± 36.718	215.25 ± 25.600
(CV%)	(23.3%)	(11.9%)
AUC_{0-t} (h*ng/mL), mean ± SD	22990.334 ± 6925.771	20124.652 ± 3495.996
(CV%)	(30.1%)	(17.4%)
$AUC_{0-\infty}$ (h*ng/mL), mean ± SD	30445.880 ± 8992.565	24622.236 ± 4671.327
(CV%)	(29.5%)	(19.0%)
T_{max}, median (range)	6.00 (5.00, 10.0)	5.50 (3.00, 9.92)
$T_{1/2}$, mean ±SD	244.713 ± 105.210	196.069 ± 34.800
(CV%)	(43.0%)	(17.7%)
CL/F (L/h), mean ± SD	0.366 ± 0.149	0.419 ± 0.080
(CV%)	(40.6%)	(19.0%)
V_z/F (L), mean ± SD	119.326 ± 40.475	116.291 ± 16.417
(CV%)	(33.9%)	(14.1%)

CL/F, apparent clearance; CV, coefficient of variation; $T_{1/2}$, terminal half-life; T_{max}, time to maximum plasma concentration; V_z/F, apparent total volume of distribution.
*One participant in the moderate hepatic impairment population did not have blood samples collected past the 48-hour blood draw and was not included in the PK population.

Figure 1. Arithmetic mean concentration ± SD by time (linear scale) in the PK population* for subjects with moderate hepatic impairment and matched volunteers with normal hepatic function



*One participant in the moderate hepatic impairment population did not have blood samples collected past the 48-hour blood draw and was not included in the PK population.

Table 3. Analysis of obicetrapib PK parameters in the PK population* for subjects with moderate hepatic impairment and matched volunteers with normal hepatic function†

PK Parameter (unit)		Moderate Hepatic Impairment (n=9)	Normal Hepatic Function (n=8)
C_{max} (ng/mL)	LS GM (SE)	153.16 (1.07)	213.96 (1.07)
	LS GM Ratio (90% CI)		71.58 (60.23, 85.07)
AUC_{0-t} (h*ng/mL)	LS GM (SE)	22100.921 (1.086)	19865.561 (1.091)
	LS GM Ratio (90% CI)		111.25 (90.12, 137.34)
$AUC_{0-\infty}$ (h*ng/mL)	LS GM (SE)	29018.991 (1.100)	24237.058 (1.106)
	LS GM Ratio (90% CI)		119.73 (93.87,152.72)

GM, geometric mean; LS, least squares; SE, standard error.
*One participant in the moderate hepatic impairment population did not have blood samples collected past the 48-hour blood draw and was not included in the PK population.
†Natural log (ln) transformation was applied to the PK parameter data prior to analysis. The estimated mean difference and associated 90% CI was back-transformed to provide GM ratios and CIs. An analysis of variance model was fitted with ln-transformed PK parameters as the dependent variable and cohort as fixed effect. LS GM ratios were estimated by moderate hepatic impairment vs normal hepatic function.

CONCLUSIONS

- **Moderate hepatic impairment modestly increased total exposure (AUC) and prolonged half-life, with lower C_{max} but similar T_{max}**
- **Obicetrapib was well tolerated by all participants in this study with no difference in TEAEs between participants with moderate hepatic impairment and healthy controls**
- **Based on these findings, no dose adjustment of obicetrapib is anticipated for patients with moderate hepatic impairment**

DISCLOSURES

JK, MD, AH, DK, and EW: Employee & Shareholders of NewAmsterdam Pharma; TS: employee of Nucleus Network; EL: Researcher for 89Bio Inc., Akero Therapeutics, Alnylam Pharmaceuticals Inc., Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Cour Pharmaceuticals, Corcept Therapeutics, Eli Lilly and Company, Enanta Pharmaceuticals, Enyo Pharma, Exalenz Bioscience, Galectin Therapeutics, Galmed Pharmaceuticals, Genfit, Gilead Sciences, GlaxoSmithKline, Hanmi Pharmaceuticals, Hightide Biopharma, Intercept Pharmaceuticals, Inventiva, Ipsen, Janssen Pharmaceuticals, Madrigal Pharmaceuticals, Merck & Co., NewAmsterdam Pharma, NGM Biopharmaceuticals Inc., Northsea Therapeutics, Novartis, Novo Nordisk Inc., Organovo, Poxel Co., Regeneron, Sagimet Biosciences, Takeda, Terns Pharmaceuticals, Viking Therapeutics, Zydus Pharmaceuticals.

1. Kastelein JJP et al. *Curr Atheroscler Rep.* 2024;26(2):35-44. **2.** U.S. Dept of Health and Human Services, Food and Drug Administration. Pharmacokinetics in patients with impaired hepatic function: study design, data analysis, and impact on dosing and labeling. Published May 2003. Accessed March 28, 2026. https://www.fda.gov/media/71311/download **3.** Data on File. NewAmsterdam Pharma.

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